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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
IBRAHIM, MEDINA AHMED	

ART UNIT	PAPER NUMBER
1638	12

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/090,035	SIMMONS, CARL R.	
	Examiner	Art Unit	
	Medina A Ibrahim	1638	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *5-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-4, and invention A (SEQ ID NO: 1-2) in Paper Nos. 10 and 11, filed on 5/27/03 and 6/17/03 with the supplemental amendment is acknowledged. The traversal is on the ground(s) that the restriction requirement between the sequences of invention (A-E) should be treated under linking claim practice as required by 37 CFR 1.141 and MPEP 809.02 because the sequences share structural and functional relationship, and asserts that claim 1 is generic for all the sequences and should be treated as a claim linking to all claims reciting individual sequences. Applicant argues that the claimed maize sequences (A-E) are functionally related and share at least from 75% to 99% of sequence identity. Applicant provides sequence alignment between SEQ ID NO: 1, 3, 5, 7, and 9 to support this position. Applicant also provides a consensus sequence common to maize sequences. Applicant requests that the restriction requirement between SEQ ID NO: 1, 3, 5, 7, and 9 be treated as species election, and urges that claims 1-4 and 13-17 be examined under the linking claim practice.

This is not found persuasive because the claimed sequences (A-K) are considered independent and distinct inventions rather than species, for the reasons of record as set forth in the last Office action. In addition, original claim 1 was directed to a group of polynucleotide sequences having specified and non-specified sequences and variants from various sources having no known function, and therefore, the claim was

not linking or generic. Claim 1 is now amended to recite a single sequence, and claims 13-17 are independent claims drawn to specific polynucleotide sequences.

However, since Applicant has shown the structural relationship between SEQ ID NO: 1, 3, 5, 7, and 9 (A-E) from maize by sequence alignment, it has been determined that the co-examination of SEQ ID NO: 1, 3, 5, 7, and 9 will not create a search burden upon the Office. Therefore, SEQ ID NO: 1, 3, 5, 7 and 9 and nucleotide sequences encoding SEQ ID NO: 2, 4, 6, 8 and 10 will be examined on the merits in this application. Applicant should note that the current PTO policy does not allow the examination of more than 10 sequences in a single application because databases and resource allocations at the PTO have changed, and the examination of all the sequences in this application would present a burden upon the PTO resource. The requirement is still deemed proper and is therefore made FINAL.

The preliminary amendments A and B have been entered. New claims 13-17 have been added. Therefore, claims 1-17 are pending.

Claims 1-4 and 13-17 and SEQ ID NO: 1-10 are under examination.

Claims 5-12 and SEQ ID NO: 13-24 are withdrawn from consideration as being drawn to a non-elected invention.

Drawings

2. No drawings are filed with this application.

Specification

3. The disclosure is objected to because of the following informalities: for example, page 17, line 26, of the specification contains an embedded hyperlink directed to an

internet address. The use of hyperlinks and/or other form of browser- executable code are not permitted under USPTO current policy because the content of such links are subject to a change, resulting in the introduction of New Matter into the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.

Claim Objections

4. Claim 3 is objected to for lacking proper article. It is suggested that "a" after "comprising" be changed to ---the---.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-4 and 13-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible utility or a well-established utility.

The claims are drawn to an isolated nucleic acid comprising a polynucleotide having at least 75% sequence identity to SEQ ID NO: 1 and encoding a maize AFP1 protein protein, a vector, a recombinant expression cassette comprising a promoter operably linked to said nucleic acid in sense or antisense orientation, and a host cell comprising said recombinant expression cassette. The claims are also drawn to polynucleotide sequences of SEQ ID NO: 1, 3, 5, 7, and 9 or complements thereof, and polynucleotide sequences encoding SEQ ID NO: 2, 4, 6, 8 and 10.

Applicant asserts that the polynucleotides of SEQ ID NO: 1, 3, 5, 7, and 9 encoding SEQ ID NO: 2, 4, 6, 8, and 10 have the utility of encoding a polypeptide

having antifungal activity. However, based upon Applicant's disclosure, the claims do not meet the utility requirements under the current utility guidelines for the following reasons: a) the predicted function is based solely upon sequence comparison with an antifungal protein from a fly from the prior art (pages 69-70, Example 3); b) no domain responsible for antifungal activity has been disclosed in SEQ ID NO: 2, 4, 6, 8, or 10; c) no data that relates any of the disclosed sequences to antifungal proteins has been disclosed; d) the only working example disclosed in the specification fails to establish antifungal activity by Applicant's sequences.

The specification, on page 70, Applicant states that SEQ ID NO: 2 shares a similar domain with a fly (*Sarcophaga pergrina*) antifungal protein and shares an overall amino acid identity of 21-25% and similarity reaching 50%. However, the state of the art teaches that sequence homology alone is insufficient to determine the functional activity of a protein. For example, an article from Science Journal (vol. 292, pp. 1486-1487, 2001(U)) reveals plant and animal genes that share an overall secondary structure and six domains of functional importance, which are still sufficiently divergent in that their function cannot be determined by sequence similarity alone. Bork et al (Genome Research, Vol. 10, 2000, pp. 398-400 (v)) also cautions using sequence comparison to predict protein function because of known error margins for high throughput computational methods (see page 398, columns 1-3; page 399, col.3 and paragraph bridging columns 2 and 3). Therefore, sequence homology alone cannot be used to determine protein function. In addition, while Applicant asserts that SEQ ID NO: 1 has antifungal activity, a sequence search result reveals that SEQ ID NO: 1 has 75%

sequence identity and similarity of 96.9% with EST sequences from salt stressed maize cDNA library (Wang et al, 2002, Sequence Search Result, pages 2- 3, Accession no. BQ619337 (W)). Therefore, it is apparent that further research not considered to be routine would be required before one skilled in the art would know how to use Applicants' SEQ ID NO: 1, 3, 5, 7, and 9 to achieve a desired trait in a host cell. Therefore, the immediate use of the claimed sequences is unclear.

While a protein having antifungal activity would have substantial utility to the public, Applicants' claimed invention is not refined and developed to the point where it would have an immediate benefit to the public. Therefore, one skilled in the art cannot readily take Applicant's claimed invention and achieve the asserted utility, based upon Applicant's disclosure.

Regarding the claims drawn to a polynucleotide having at least 75% sequence identity to SEQ ID NO: 1, since SEQ ID NO: 1 encoding SEQ ID NO: 2 does not have utility as discussed above, sequences less than 100% sequence identity thereof would not have utility.

Furthermore, there is no well-established utility for the claimed sequences, since there is no utility for probes, primers or antibodies to the expressed protein of a polynucleotide having no known function. Therefore, in view of the reasons set forth above, the claimed sequences do not have a real-world use and, therefore, the claimed invention lacks utility.

Claim R jections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-4 and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant teaches isolation and sequencing of five full-length cDNAs termed as alleles from maize leaves inoculated with a fungal pathogen (Examples 1-2). Applicant states that the five cDNAs represent a disease or stress-induced polynucleotide and teaches that the five cDNAs encode either identical or nearly identical peptides. Applicant shows that the expression of the coding region of ZmAFP1-1 (SEQ ID NO: 1 encoding SEQ ID NO: 2) in *E.coli* resulted in a protein with no antifungal activity against several maize fungal pathogens (Example 3). Applicant also teaches prophetic methods of transforming and regenerating transgenic plants including maize, soybean, and sunflower containing AFP1 (Examples 4-5).

The claimed invention, namely, isolated polynucleotide sequences of SEQ ID NO: 1, 3, 5, 7, and 9, or sequences having at least 75% sequence identity to SEQ ID NO: 1 and encoding a maize AFP1 protein antifungal protein is not supported by enabling disclosure because the specification has not disclosed or established any antifungal activity by the claimed sequences.

The state of the prior art as exemplified by Van Loon et al (Physiol. and Molecul. Plant Pathol. Vol. 55, pp. 85-97, and 1999(X)) teaches the criteria of identifying defense related proteins and discusses as follows: "(i) protein(s) must be induced by a pathogen in tissues that do not normally express the protein(s), and (ii) induced expression must have been shown to occur in at least two different plant pathogen combinations (page 85, paragraph bridging columns 1 and 2). None of the claimed sequences are induced by at least two pathogens. While the state of the prior art discloses several plant antifungal and antimicrobial proteins including Rs-AFP1 from *Raphanus sativum*, Bn-AFP1 from Brassica napus, Br-AFP1 from Brassica rapa, At-AFP1 from *Arabidopsis thaliana,* DM-AMP1 from *Dahlia merck*, etc, a sequence search result of SEQ ID NO: 2, 4, 6, 8, and 10 reveals no homology with the prior art plant antifungal or antimicrobial proteins.

In addition, the only working example disclosed in the specification fails to establish AFP1 activity by the claimed sequences.

Therefore, given the lack of antifungal activity by the claimed polynucleotides, the state of the prior art, the nature of the invention, and unpredictability with respect predicting the function of a protein by sequence alignment, one skilled in the art would not be able to use the claimed sequences to transform a host cell for a desired phenotype, without undue experimentation.

In the event that Applicant provides evidence to show the antifungal or antimicrobial activity by SEQ ID NO: 1, 3, 5, 7, and 9, a scope of enablement rejection would still be maintained for claims drawn to a polynucleotide having at least 75%

sequence identity to SEQ ID NO: 1 and the antisense polynucleotide thereof encoding a maize AFP1 protein.

The claimed polynucleotides having at least 75% sequence identity encompass modified sequences obtainable by multiple deletions and/or substitutions of nucleotides in SEQ ID NO: 1. However, Applicant has not provided guidance with respect to which regions in SEQ ID NO: 1 would tolerate such modifications.

While mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims. One skilled in the art would expect any tolerance to modification for a given DNA to diminish with each further and additional modification or multiple substitutions/ deletions. One skilled in the art would have to make all possible nucleotide substitutions and deletions in SEQ ID NO: 1 and test all polynucleotides that meet the structural limitation to determine which also meet the functional limitation.

The state of the prior art teaches unpredictability inherent in DNA/protein function if one or more bases/amino acids in that DNA/protein are modified. For example, Lazar et al (Molecular and Cellular Biology, March 1988, Vol. 8, No. 3, pp. 1247-1257 (U)) teach that a mutation of aspartic acid 47 and leucine 48 of a transforming growth factor alpha results in different biological activities (see at least the Title). Broun et al (Science, 13 November 1998, vol. 282, pp. 131-133 (V)) teach that as few as four amino acid substitutions in a protein can change the protein activity (Abstract). Note, the nucleotide sequences encoding the proteins (mutated and original) disclosed by either Lazar or Broun would share more than 75% sequence identity. Therefore, it is unpredictable if

any polynucleotide sequence having at least 75% to SEQ ID NO: 1 would encode a maize AFP1 protein, without undue experimentations. Further, Applicant has not provided guidance for how to use the antisense of SEQ ID NO: 1.

Therefore, given the given the breadth of the claims, the lack of guidance, the state of the prior art, nature of the invention, and unpredictability with respect to protein modifications, the claimed invention is not enabled throughout the broad scope. See In re Wands 858 F.2d 731, 8USPQ2nd 1400 (Fed. Cir, 1988).

See, also, *Amgen Inc. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at 1027 (Fed. Cir. 1991) where the court held that the disclosure of a few gene sequences did not enable claims broadly drawn to any analog thereof.

Written Description

9. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a multitude of polynucleotide having at least 75% sequence identity to SEQ ID NO: 1 and encoding a maize AFP1 protein, vectors, expression cassettes, and host cells comprising said polynucleotides.

Applicant has not described a polynucleotide having at least 75% sequence identity to SEQ ID NO: 1 and that encodes a maize AFP1 protein. While SEQ ID NO: 3, 5, 7, and 9 meet the claimed structural limitation, no antifungal or other antimicrobial function has been established for any of the disclosed sequences. Therefore, a mere

recitation of a functional limitation in the claims would not provide adequate written description for the claimed invention. In addition, since Applicants has not described a polynucleotide having at least 75% sequence identity to SEQ ID NO: 1 that encodes a maize AFP1 protein as discussed above, vectors, expression cassettes, and host cells comprising said polynucleotide are similarly not described. Consequently, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that one skilled in the art would recognize that Applicants are in possession of the invention as broadly claimed. See Written description Examination Guidelines published in Federal Registry/Vol. 66, No.4/Friday, January 5, 2001/Notices). See, also *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997).

Remarks

10. Claims 1-4 and 13-17 are free of the prior art of record because the prior art does not teach or suggest isolated nucleic acids comprising the polynucleotide sequence of SEQ ID NO: 1, 3, 5, 7, 9, and a polynucleotide having at least 75% sequence identity to SEQ ID NO: 1 that encodes a maize AFP1 protein.

11. No claim is allowed.

12. Papers related to this application may be submitted to Technology Sector 1 by facsimile transmission. Papers should be faxed to Crystal Mall 1, Art Unit 1638, using fax number (703) 308-4242. All Technology Sector 1 fax machines are available to receive transmission 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Medina A. Ibrahim whose telephone number is (703)

306-5822. The Examiner can normally be reached Monday-Thursday from 8:30AM to 5:30PM and every other Friday from 9:00AM to 5:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Amy Nelson, can be reached at (703) 306-3218.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

7/10/03
Mai

Mark A. Wardle